Interdependence of Physiological Surfactant and Drug Particle Size on the Dissolution Behavior of Water-Insoluble Drugs

By SONG-LING LIN, JOHANNE MENIG, and LEON LACHMAN

A series of *in vitro* experiments was performed to demonstrate the interdependence of physiologic surfactant and drug particle size on the dissolution rate of glutethimide, griseofulvin, and a new diuretic Compound A. The presence of physiological concentrations of lysolecithin (a naturally occurring biosurfactant) is shown to exhibit micellar solubilizing properties on the drugs investigated. The data obtained from the dissolution rate studies showed that aqueous lysolecithin solution caused significant enhancement of the extent of solution of the drugs investigated. However, the reduction of particle size through micronization may not necessarily increase the *in vitro* dissolution rate. Data to support this statement are presented, and a plausible explanation for its occurrence is the electrostatic charge that develops on the solids after milling. This results in aggregates which can be larger in particle size than the unmilled drug.

SURFACE-ACTIVE AGENTS are commonly used as adjuvants in pharmaceutical preparations. Through the reduction of interfacial tension and micelle formation, these materials are capable of enhancing the aqueous solubility of poorly soluble drugs.

In biological systems, naturally occurring physiological surfactants are present in various tissues and organs at varying levels of concentration. There are a number of literature reports pertaining to the micellar solubilizing properties of physiologic surfactants for water-insoluble or slightly soluble medicinal agents. The physiologic surfactants most extensively employed in studying drug solubilization and dissolution are the bile salts. It has been shown that various bile salts are capable of solubilizing strychnine, quinine, quinoline, and camphor (1), dyes (2, 3), steroid hormones (4–6), carcinogenic polycyclic hydrocarbons (7–9), fatty acids, monoglycerides and cholesterol (10–14), glutethimide, griseofulvin and hexestrol (15), and inorganic salts (1).

In 1959 Robinson and Saunders (16) reported on the micellar solubilizing characteristics of the nonionic surfactant lysolecithin with triolein, monostearin, and cholesterol. More recently it was reported that lysolecithin exhibited marked solubilizing properties for and increased the dissolution rates of dienestrol, hexestrol, and griseofulvin (17).

It is generally believed that in order for a solid drug to be absorbed to any appreciable extent across the gastrointestinal membrane, it is preferable to have the drug go into solution in the gastrointestinal fluid prior to the absorption process. The rate-determining step in the diffusion-controlled absorption process for orally administered water-insoluble drugs is usually the dissolution rate of drugs in the biological fluids of the gastrointestinal tract. The significance of this on the transport and absorption processes is well recognized and has been the subject of several detailed discussions (18–21).

The factors influencing the dissolution rate are many and varied but one important factor is the surface characteristics of the solid particles (22–25). Following the disintegration of tablet and capsule dosage forms in the gastrointestinal tract, the particles break down into their initial particulate state or form small aggregates of drug. The surface characteristics of these aggregates would be different from the individual particles of drug and their subsequent dissolution behaviors would not be the same as for nonaggregated drug particles. Since most of the dissolution studies performed in the presence of physiologic surfactants have been reported to have been carried out without controlling the particle size of the medicinal agent, the present investigation was undertaken to study the influence of varying degrees of available surfaces on the dissolution rate of glutethimide, griseofulvin, and a new diuretic Compound A. The dissolution rate was determined in distilled water, 0.1 *N* hydrochloric acid, and 0.05% w/v aqueous lysolecithin solution at 37°.

EXPERIMENTAL

Materials—Glutethimide NF was dried at 45° over phosphorus pentoxide and was used without further purification. Analysis by NF assay (26)

Received June 19, 1968, from the Development and Control Dept., Ciba Pharmaceutical Co., Summit, NJ 07901
Accepted for publication August 20, 1968.
Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Miami Beach meeting, May 1968.
The authors would like to express their gratitude to Miss Ann Nolan for her valuable assistance.

indicated a purity of better than 99.95%. Part of the samples were sieved through U. S. standard sieves and fractions of 20/40 and 100/120 mesh particles were collected for use in this investigation. The remaining material was micronized through a fluid energy mill[1] to obtain material less than 5 μ in size.

The new diuretic Compound A was dried at 100° for 8 hr. Analysis by a nonaqueous titrimetric method indicated a purity of better than 99%, which was substantiated by TLC analysis. Samples consisting of material being less than 5 μ and particles of 12/16 and 60/80 mesh were prepared as described for glutethimide.

Griseofulvin,[2] micronized and nonmicronized, was used as received. The nonmicronized powders were sieved and the particles of 12/16 and 20/40 mesh were employed in this study.

Lysolecithin[3] was reported to be better than 99% pure by paper chromatographic analysis. Elemental analysis of the lysolecithin sample was reported previously (17). The sample was dried in vacuum for at least 24 hr. prior to use.

Analytical Method—Beer's law curves were constructed individually for glutethimide (256 mμ), diuretic Compound A (282 mμ), and griseofulvin (292.5 mμ). The solvent systems employed were methanol–water in the ratio of 1:4, 1:1, and 3:2 for glutethimide, diuretic Compound A, and griseofulvin, respectively. In the dissolution rate determination the concentration of lysolecithin present in the diluted sample aliquots was found not to interfere with the spectrophotometic assay at the aforementioned wavelengths. A Beckman DB spectrophotometer with a Sargent recorder was used to obtain absorbance readings throughout the study.

Determination of Dissolution Rate—The procedures of Shefter and Higuchi (27) were employed with slight modification. A quantity of drug, in large excess of its predetermined solubility in 0.05% w/v aqueous lysolecithin solution was weighed and rapidly introduced to a 250-ml. water-jacketed beaker containing exactly 100 ml. of dissolution medium maintained at 37 ± 0.5°. The solution was agitated by means of an overhead stirrer. The three-blade stirrer was 2.5 cm. in diameter and located 2 cm. below the surface of dissolution medium. Constant agitation intensity was achieved by utilizing a constant torque unit (Servodyne). In order to insure complete contact of the hydrophobic drug with the fluid of the dissolution medium, a relatively high intensity of agitation, 600 r.p.m., was employed throughout the study. Water, 0.1 *N* hydrochloric acid, or 0.05% w/v aqueous lysolecithin solution was used as the dissolution medium. A 5-ml. aliquot was withdrawn at prescribed time intervals from the dissolution flask and replaced immediately with the same volume of dissolution medium maintained at 37°. The aliquot was rapidly filtered through 0.45-μ pore size Millipore filter paper to remove remaining undissolved drug. The clear filtrate was assayed spectrophotometrically after proper dilution with appropriate solvent. A cumulative correction was made in accordance with the method reported by Wurster and Taylor (28) to account for the previously removed samples in determining the total amount of drug dissolved at any specific time.

The photomicrographs of the drugs before and after the dissolution study were taken with a Polaroid camera attached to the photomicrographic apparatus.[4]

Electrostatic Charge of the Powders—The electrostatic properties of the various sized fractions of glutethimide, diuretic Compound A, and griseofulvin were determined at 37% R.H. and 25° using the apparatus and procedure described in an earlier publication (29).

RESULTS AND DISCUSSION

The solubilization of a water-insoluble drug, *D*, in the presence of surfactant can be treated as a process in which the drug is distributed between a micellar phase and an aqueous phase. Above the CMC of a surfactant, the solution is saturated with respect to surfactant monomers and an equilibrium exists between monomers and micellar aggregates. Therefore, the following equilibrium state can be written:

$$D_{\text{solid}} \rightleftarrows D_M + D_{NM} \qquad \text{(Eq. 1)}$$

where D_M is the concentration of drug in micelle and D_{NM} is the drug concentration in the nonmicellar phase. The equilibrium is influenced not only by the parameters of temperature, pressure, and surfactant concentration, but also by the characteristics of the solid particles employed. The reduction of particle size results in an increase of available surface area as well as a considerable increase in surface free energy. In general, the smaller the particle size of the solid, the greater is the shift of the equilibrium to the right-hand side of Eq. 1. This phenomenon of increasing solubility with decreasing particle size has been reported (30–32). The importance of identifying the characteristics of the physical state of the solid in solubility measurement as well as in the determination of dissolution rate is evident.

Figure 1 demonstrates the dissolution behavior of diuretic Compound A using 12/16 mesh, 60/80 mesh, and micronized powders, in water and 0.05% aqueous lysolecithin solution at 37°, respectively. Each curve is drawn through points which represent an average of at least two dissolution runs. In all instances the reproducibility is within the experimental error. It can be seen from these curves that the presence of lysolecithin in the dissolution medium significantly enhances the extent as well as the rate of dissolution of diuretic Compound A when compared to the extent and the rate of dissolution found in water. Since the dissolution rate is directly proportional to the solubility term in the Noyes-Whitney equation, the modification of the nature of the dissolution media which will effectively increase the solubility term should increase the dissolution rate. The ratio of the quantity of the solubilized drug in lysolecithin to the quantity of drug in water at the same time interval is expressed as relative extent of dissolution. As shown in Table I the lysolecithin micelle displays

[1] Trost Jet Mill, Helme Products Inc., Helmetta, N. J.
[2] Generously supplied by Dr. H. Wolkoff, Schering Corp., Bloomfield, N. J.
[3] Purchased from Nutritional Biochemicals Co., Cleveland, Ohio.
[4] Phaphot, Ernest Leitz Ltd., Germany.

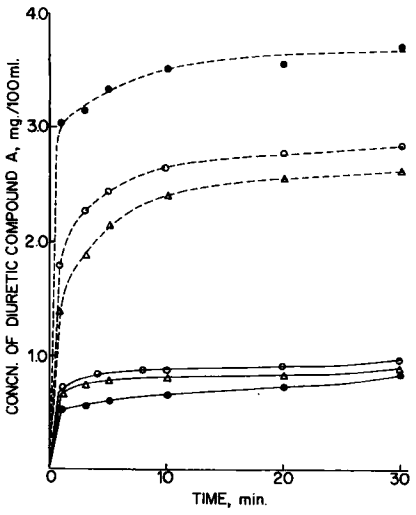

Fig. 1—Dissolution profiles of diuretic Compound A in water (——) and 0.05% aqueous lysolecithin solution (···) at 37°. Key: ●, micronized powder; ○, 60/80 mesh powder; △, 12/16 mesh powder.

approximately threefold increase in relative extent of dissolution for the 12/16 and 60/80 mesh powders of diuretic Compound A, while about fivefold increase was observed for micronized diuretic Compound A during the time period of 10–30 min. The ratio persists even after 2 hr. The enhancement in the extent as well as the rate of dissolution in the presence of lysolecithin is due to the lowering of the interfacial tension between the drug and the dissolution medium, as well as to micellar solubilization. The latter mechanism is most likely more significant since the concentration of lysolecithin employed in the dissolution rate determination is much higher than the CMC of lysolecithin.

As expected, the reduction of particle size from 12/16 mesh to 60/80 mesh slightly increases the extent of dissolution behavior of diuretic Compound A in water and 0.05% lysolecithin solution. However, when the particle size is further reduced to the micron range, the extent of dissolution of diuretic Compound A in water decreases somewhat when compared with the 12/16 or 60/80 powders. The probable explanations for these surprising results are (*a*) that the hydrophobic properties of the powder increases with the degree of subdivision of the powders because of absorption of air caused by micronization, and (*b*) the relative magnitude of the interparticulate binding force, such as electrostatic charge, is increased as the particle size is greatly reduced. Clumping of the diuretic Compound A micronized particles was observed during the dissolution experiments. Large particulate agglomerates, some being larger in particle size than the unmilled drug, were found to persist in the water even after 2 hr. of dissolution study. As shown in photomicrographs A and B of Fig. 2, the micronized sample observed after a 2-hr. dissolution run in water is present as aggregates having diameters larger than the 60/80 mesh powders. The measurement of the electrostatic charge of the various particle sizes of diuretic Compound A indicated that the electrostatic charge of the powders increased with increasing surface area through particle size reduction (33).

When 0.05% lysolecithin solution was employed as the dissolution medium, the dissolution rate of diuretic Compound A increased with the decreasing particle size as illustrated by the upper three curves of Fig. 1. This difference in effect of dissolution in water and lysolecithin solution can be explained by the surfactant wetting the hydrophobic surface of diuretic Compound A and breaking the large particle agglomerates into their original individual particulate state. This is illustrated with photomicrographs A and C or B and D of Fig. 2. The interparticulate interactions observed in photomicrograph B are reduced greatly in the presence of lysolecithin, as demonstrated in photomicrograph D of Fig. 2. This accounts for the fact that micronized diuretic Compound A exhibits a greater extent of dissolution than the unmilled powder in lysolecithin solution but not in water. The photomicrographs were taken of the samples before filtration through the Millipore assembly. If the photomicrographs are taken on the filtered powders upon dispersion in a suitable medium, such as mineral oil, it is not realistic of the state of the micronized drug during the dissolution run.

A similar phenomenon was observed for griseofulvin. The dissolution behaviors of micronized, 20/40, and 12/16 mesh samples of griseofulvin are depicted in Fig. 3. The extent of dissolution is increased at least twofold, when the dissolution medium is changed from water to 0.05% lysolecithin solution.

Inspection of the data in Table I shows that after 10 min., the ratios of the amount of drug dissolved in the 0.05% lysolecithin solution to that amount dissolved in water are 2.3, 2.1, and 2.4 for 12/16 mesh, 20/40 mesh, and micronized griseofulvin, respectively.

Table I—Relative Extent of Dissolution at 37°

Compound	Particle Size	Relative Extent of Dissolution[a] Time, min. 1	2	5	10	20	30
Diuretic Compound A	12/16 mesh	2.12	2.65	2.74	3.00	3.08	2.89
	60/80 mesh	2.50	2.37	2.52	2.98	3.04	2.96
	Micronized	5.81	5.55	5.39	4.86	4.97	4.86
Griseofulvin	12/16 mesh	5.11	3.47	2.64	2.28	2.29	2.32
	20/40 mesh	2.01	2.05	2.16	2.13	2.17	2.25
	Micronized	2.68	2.62	2.40	2.38	2.41	2.46
Glutethimide	20/40 mesh	1.00	1.02	1.01	1.01	0.99	1.01
	100/120 mesh	1.12	1.14	1.10	1.07	1.09	1.09
	Micronized	1.03	1.03	1.01	1.00	1.01	1.02

[a] Ratio of the quantity of solubilized drug in lysolecithin to the quantity of drug in water at the same time intervals.

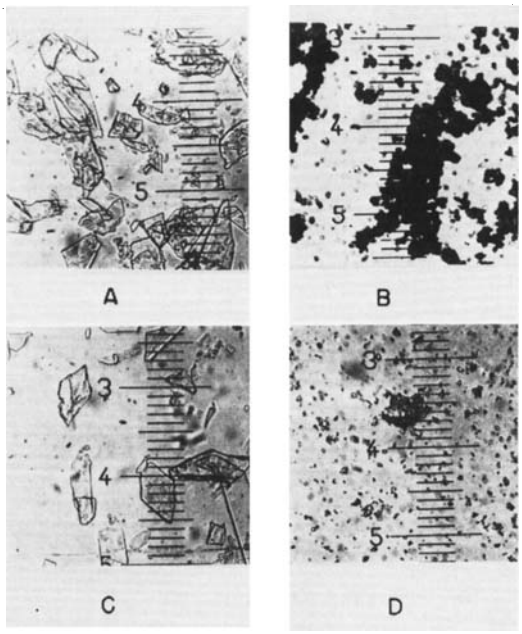

Fig. 2—Photomicrographs illustrating the physical state of diuretic Compound A after 2 hr. of dissolution study. Key: A, 60/80 mesh powders in water; B, micronized powders in water; C, 60/80 mesh powders in 0.05% aqueous lysolecithin solution; D, micronized powders in 0.05% aqueous lysolecithin solution.

In lysolecithin solution, the extent as well as the rate of the dissolution increases as the particle size is decreased from 12/16 mesh to micronized powder. However, in water the dissolution profile of micronized griseofulvin lies between that of 20/40 and 12/16 mesh samples.

It has been reported that when micronized griseofulvin is used, the blood levels can be achieved with approximately half the dose of the larger particle size material (34). Thus it is clear that the increase of *in vivo* drug availability in the biological system through particle size reduction may not readily be predicted by *in vitro* dissolution studies in aqueous systems. This is especially true when the dissolution rate of the water-insoluble hydrophobic drug is studied in water. Although the addition of synthetic or naturally occurring surfactant in the dissolution medium gives a better indication of the influence of particle size reduction on increasing dissolution rate, the ultimate means of providing the evidence to demonstrate that particle size reduction decreases the dose needed to produce an equal pharmacological response is by *in vivo* rather than *in vitro* study.

An interesting dissolution behavior was observed for glutethimide. The results of the dissolution rate study in water and 0.05% lysolecithin solution are depicted in Fig. 4. The extent of dissolution at the first 10-min. period was found to decrease in the following order:

100/120 mesh > micronized > 20/40 mesh glutethimide;

whereas after 20 min. the order becomes

100/120 mesh > 20/40 mesh > micronized glutethimide.

The same trend is found in both water and 0.05% lysolecithin solution. In contrast to the common belief that the dissolution rate is increased or reaches a plateau with respect to the decreasing particle size, it seems that an optimal particle size is desirable for glutethimide since the dissolution rate increases up to a particular particle size then decreases. As discussed previously and indicated in Table I the relative extent of dissolution of diuretic Compound A and griseofulvin was considerably enhanced by the presence of lysolecithin solution. However, the dissolution rate of the 20/40 mesh and micronized glutethimide was not affected and 100/120 mesh glutethimide was increased only 10% by the incorporation of the biosurfactant as seen in Fig. 4. This case seems to be an excellent example where particle size rather than the presence of biosurfactant has the predominant effect on dissolution rate.

Photomicrographs of the glutethimide taken after the 2-hr. dissolution rate study in water and

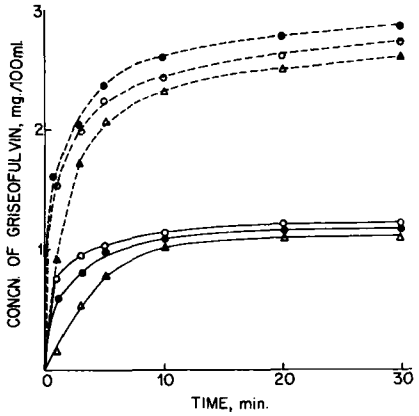

Fig. 3—Dissolution profiles of griseofulvin in water (——) and 0.05% aqueous lysolecithin solution (···) at 37°. Key: ●, micronized powder; ○, 20/40 mesh powder; △, 12/16 mesh powder.

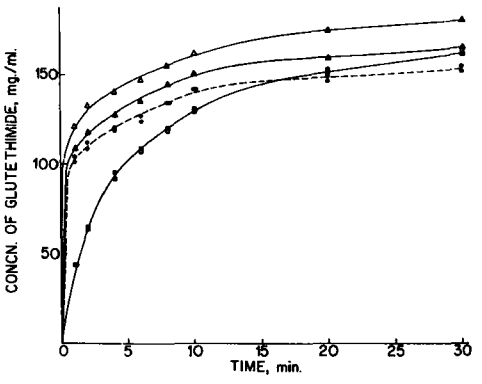

Fig. 4—Dissolution profiles of glutethimide in water (closed symbols) and 0.05% aqueous lysolecithin solution (open symbols) at 37°. Key: ○, ●, micronized sample; △, ▲, 100/120 mesh sample; □, ■, 20/40 mesh sample.

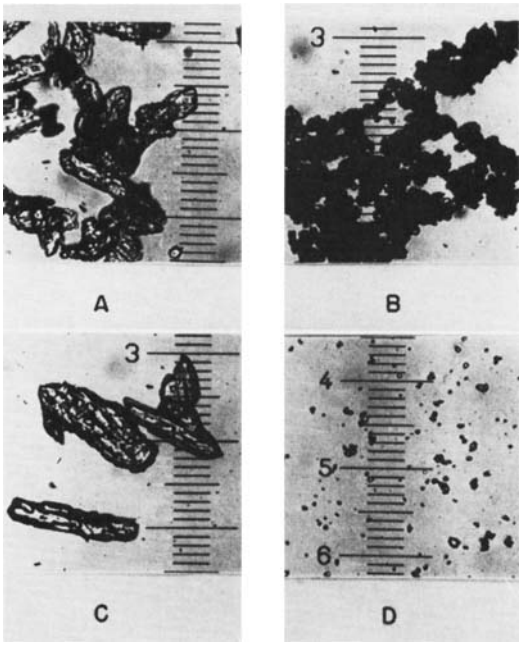

Fig. 5—Photomicrographs illustrating the physical state of glutethimide after 2 hr. of dissolution study Key: A, 20/40 mesh powders in water; B, micronized powders in water; C, 20/40 mesh powders in 0.05% aqueous lysolecithin solution; D, micronized powders in 0.05% aqueous lysolecithin solution.

0.05% lysolecithin solution are shown in Fig. 5. The decrease in the dissolution rate by changing from 20/40 mesh powder to micronized glutethimide as shown in Fig. 4 can be attributed to the fact that the particulate agglomerates of the micronized sample (photomicrograph B, Fig. 5) are larger in size than the 20/40 mesh particles (photomicrograph A, Fig. 5). When 0.05% lysolecithin solution is employed, the hydrophobic surface of glutethimide is wetted by the surfactant and the particulate agglomerates were dispersed to their individual particles as shown in photomicrographs C and D of Fig. 5. However, a corresponding increase of the dissolution rate was not observed. A possible explanation for this phenomenon may be the fact that micellar aggregates of lysolecithin have little affinity for glutethimide, as demonstrated by the equilibrium solubility curve of Fig. 6. The equilibrium solubility of glutethimide in 0.05% aqueous lysolecithin is increased only 15% as compared with the equilibrium solubility of glutethimide in water. It has been demonstrated, *in vivo*, that the blood level of glutethimide is not influenced by the reduction of particle size. On the contrary, griseofulvin which exhibits a particle size effect on the blood levels of griseofulvin has an equilibrium solubility of 0.024% in 0.05% aqueous lysolecithin solution which is about 70% higher than that in water (17). It seems that the higher the extent of interaction between the drug and biosurfactant, the greater the dependency of the drug concentration in the blood on the particle size of the drug.

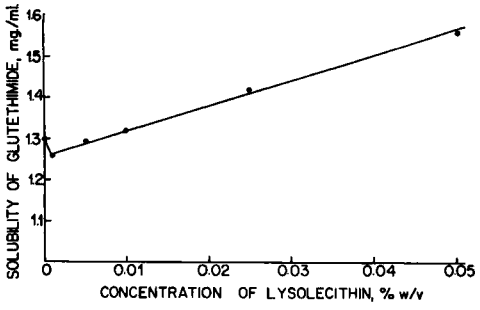

Fig. 6—Solubilization of glutethimide in aqueous lysolecithin solutions at 37°.

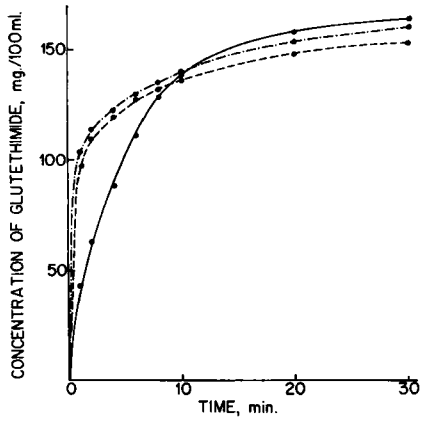

Fig. 7—Dissolution profiles of glutethmide in 0.1 N hydrochloric acid at 37°. Key: —, micronized powder; -·-, 100/120 mesh powder; ——, 20/40 mesh powder.

Since glutethimide is available commercially as a solid dosage form, the effect of particle size on the dissolution rate of glutethimide in 0.1 *N* hydrochloric acid at 37° was investigated. The results are graphically shown in Fig. 7. As observed previously for the dissolution rate in water and lysolecithin, the micronized glutethimide does not appear to go into solution faster than 100/120 mesh sample. However, the dissolution rate is increased significantly at the first 5-min. period of the dissolution run when the micronized or 100/120 mesh glutethimide is used in place of the 20/40 mesh material.

The physicochemical approach for investigating the nature of the interactions of water-insoluble drugs with normal constituents of the biological system is believed to contribute significantly to a greater understanding of the complexity of absorption, transport, interaction, and excretion of the drug in the living system. There exist certain physiologic surfactants either as normal constituents of the biological fluids or resulting from the discharge into a particular compartment or compartments of the biological system. Typical examples of these are lecithin, lysolecithin, and bile salts (35–40) which appear in the pancreas, duodenal fluid, and blood stream. As a result of the findings in this investigation and those from previous reports (17) the presence of naturally occurring physiologic surfactants, such as lysolecithin in the biological system can possibly increase the extent as well as the rate of dissolution of water-insoluble medicinal agents prior to the absorption process.

Presently under study is the influence of other physiologic surfactants, such as α-cephalin, phosphatidyl ethanolamine, and phophatidyl serine as well as phosphatidyl inositol on the dissolution properties of poorly soluble drugs, and information being obtained will be presented in a subsequent report.

CONCLUSION AND SUMMARY

The interdependence of physiologic surfactant and drug particle size on the extent and the rate of dissolution of diuretic Compound A, griseofulvin, and glutethimide was investigated. The presence of lysolecithin is generally shown to exhibit micellar solubilizing properties on the drugs investigated. From the dissolution profiles of these relatively water-insoluble drugs, the aqueous lysolecithin solution caused significant enhancement of the extent as well as the rate of solution. However, reduction of particle size through micronization does not necessarily increase the *in vitro* dissolution rate. A plausible explanation for this occurrence is the electrostatic charge that develops on the solids after milling resulting in the development of aggregates which can be larger in size than the unmilled drug.

REFERENCES

(1) Verzar, F., *Nutr. Abstr. Rev.*, **2**, 441(1933).
(2) McBain, J. W., Merrill, R. C., Jr., and Vinograd, J. R., *J. Am. Chem. Soc.*, **63**, 670(1941).
(3) Merrill, R. C., Jr., and McBain, J. W., *Ind. Eng. Chem.*, **34**, 915(1942).
(4) Ekwall, P., and Sjoblom, L., *Acta Chem. Scand.*, **3**, 1179(1949).
(5) Ekwall, P., and Sjoblom, L., *Acta Endocrinol.*, **4**, 179(1950).
(6) Ekwall, P., and Sjoblom, L., *Acta Chem. Scand.*, **5**, 1383(1951).
(7) Ekwall, P., and Setala, K., *ibid.*, **2**, 733(1948).
(8) Ekwall, P., Setala, K., and Sjoblom, L., *ibid.*, **5**, 175(1951).
(9) Norman, A., *ibid.*, **14**, 1295(1960).
(10) Ekwall, P., "Biochemical Problems of Lipids," Butterworth, London, England, 1953, p. 103.
(11) Hofmann, A. F., *Biochem. J.*, **89**, 57(1963).
(12) Hofmann, A. F., *Biochim. Biophys. Acta*, **70**, 306 (1963).
(13) Hofmann, A. F., *Nature*, **190**, 1106(1961).
(14) Hofmann, A. F., "Proc. Intern. Conf. Biochem. Probl. Lipids," 6th, 1960, p. 158.
(15) Bates, T. R., Gibaldi, M., and Kanig, J. L., *J. Pharm. Sci.*, **55**, 191, 901(1966).
(16) Robinson, N., and Saunders, L., *J. Pharm. Pharmacol.*, **11**, 346(1959).
(17) Bates, T. R., Lin, S. L., and Gibaldi, M., *J. Pharm. Sci.*, **56**, 1492(1967).
(18) Nelson, E., *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 607 (1957).
(19) Wagner, J. G., *J. Pharm. Sci.*, **50**, 359(1961).
(20) Levy, G., *ibid.*, **50**, 388(1961).
(21) Ballard, B. E., and Nelson, E., *J. Pharmacol. Exptl. Therap.*, **135**, 120(1962).
(22) Schurr, J., *J. Chim. Phys.*, **2**, 245(1904).
(23) Dundon, M. L., and Mack, E., Jr., *J. Am. Chem. Soc.*, **45**, 2479(1923).
(24) Higuchi, W. I., Parrott, E. L., Wurster, D. E., and Higuchi, T., *J. Am. Pharm. Assc., Sci. Ed.*, **47**, 376(1958).
(25) Wurster, D. E., and Seitz, J. A., *ibid.*, **49**, 335(1960).
(26) "The National Formulary," 12th ed., Mack Publishing Co., Easton, Pa., 1965, p. 177.
(27) Shefter, E., and Higuchi, T., *J. Pharm. Sci.*, **52**, 781(1963).
(28) Wurster, D. E., and Taylor, P. W., *ibid.*, **54**, 670 (1965).
(29) Lachman, L., and Lin, S. L., *ibid.*, **57**, 504(1968).
(30) May, D. R., and Kolthoff, I. M., *J. Phys. Colloid Chem.*, **52**, 836(1948).
(31) Martin, A. N., "Physical Pharmacy," Lea & Febiger Philadelphia, Pa., 1960, p. 379.
(32) Higuchi, T., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 659(1958).
(33) Lin, S. L., and Lachman, L., to be published.
(34) Atkinson, R. M., Bedford, C., Child, K. J., and Tomich E. G., *Nature (London)*, **193**, 588 (1962).
(35) Shapiro, B., *Nature*, **169**, 29(1952).
(36) Borgstrom, B., *Acta Chem. Scand.*, **11**, 749(1957).
(37) Rimon, A., and Shapiro, B., *Biochem. J.*, **71**, 621 (1959).
(38) Vogel, W. C., and Zieve, L., *J. Clin. Invest.*, **39**, 1295(1960).
(39) Magee, W. L., and Thompson, R. H. S., *Biochem. J.*, **77**, 526(1960).
(40) Zieve, L., and Vogel, W. C., *J. Lab. Clin. Med.*, **57** 586(1961).

Keyphrases

Dissolution—water-insoluble drugs
Surfactant, physiologic—dissolution, water-insoluble drug
Particle size—dissolution, water-insoluble drug
Interdependence, surfactant, particle size—dissolution
Photomicrographs—drug particles